1065-173 Effects of Pioglitazone on Endothelial Function and Aortic Stiffness in Patients With Type 2 Diabetes Mellitus

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Background: Endothelial dysfunction has been reported in patients with diabetic mellitus (DM). Insulin resistance plays an important role in the pathogenesis of endothelial dysfunction. We assessed the effects of pioglitazone on endothelial function and aortic stiffness and exercise tolerance in diabetic patients. **Methods:** Twenty patients with untreated type 2 DM were randomized to receive pioglitazone (*Piog group*: n=10, 15-30 mg/day) or not to receive pioglitazone (*Cont group*: n=10) after the standard therapy. Flow-mediated dilatation (FMD) and Nitroglycerin-induced dilatation (NID) of brachial artery were measured by using ultrasound system. We also measured aortic pulse wave velocity (PWV) to evaluate aortic stiffness by using oscilometric technique (form PWV/ABI ®, COLIN). These measurements were performed at baseline and then at 3 and 6 months after the treatment. **Results:** At baseline, there was no difference in glucose level, HbA1c, HOMA-IR, FMD, NID, and PWV between two groups. There is no difference in glucose level and HbA1c at 3 and 6 months between two groups, but HOMA-IR and systolic blood pressure were significantly decreased after 6 months in the *Piog group*. FMD was significantly increased after 3 and 6 months in the *Piog group*. PWV was significantly decreased after 6 months in the *Piog group*. NID did not change during the study in two groups. **Conclusion:** Pioglitazone improves not only insulin resistance, but also endothelial function and aortic stiffness in patients with type 2 DM.

		Baseline	3 months	6 months
Systolic BP (mmHg)	**Pioglitazone**	147+/-9	147+/-8	136+/-5***#**
	Control	146+/-8	147+/-7	148+/-6
HOMA-IR	**Pioglitazone**	2.9+/-0.4	2.2+/-0.6*****	1.8+/-0.3***#**
	Control	3.0+/-0.4	2.5+/-0.6	2.4+/-0.6
FMD (%)	**Pioglitazone**	4.9+/-1.7	7.6+/-1.4***#**	9.4+/-1.3***#**
	Control	5.2+/-1.3	5.7+/-1.1	5.5+/-1.2
NID (%)	**Pioglitazone**	14.5+/-1.1	14.5+/-0.9	14.7+/-1.3
	Control	14.1+/-1.7	13.9+/-1.2	14.0+/-1.1
PWV (cm/sec)	**Pioglitazone**	1535+/-69	1536+/-83	1369+/-53***#**
	Control	1522+/-82	1523+/-83	1519+/-75

Data are mean+/-SD. *p<0.01 vs Baseline, #p<0.01 vs Control

1065-174 Early Morning Impairment of Endothelial Function in Healthy Humans

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Background: Cardiovascular events, such as myocardial infarction, sudden death, and stroke have a peak incidence in the early hours after waking. The mechanisms involved in this circadian variation are not clear. Endothelial dysfunction is associated with increased risk for cardiovascular events. We tested the hypothesis that endothelial function is impaired in the early morning, around the time of waking, in comparison to measurements obtained both before sleep, and later in the day, in healthy humans.
Methods: We studied 28 healthy subjects (mean age: 41 years, mean body mass index: 27.8 kg/m^2, 19 male, 9 female). All participants had no history of cardiovascular or other diseases, smoking or diabetes, and were not taking any medication. All volunteers underwent polysomnography to exclude obstructive sleep apnea or other sleep disorders. Endothelial function was measured by brachial artery percent changes of diameter after ischemia, flow-mediated endothelium-dependent vasodilation (FMD), and after nitroglycerin, endothelium-independent vasodilation (non-flow mediated vasodilation-NFMD), on three different occasions; first, before the subjects went to sleep (9:00PM); second, in the morning immediately after waking (6:00AM); and third, during the late morning, five hours after waking (11:00PM).
Results: Values are expressed as mean ± SE. All subjects had normal sleep with good sleep efficiency of 84 ± 2.3 %. Compared to prior to sleep, FMD decreased markedly in the early morning after waking, and recovered by late morning (9:00PM: 6.8 ± 0.8%; 6:00AM: 4.4 ± 0.7%; 11:00AM: 7.04 ± 0.7%; p=0.035). NFMD was similar for the three periods of observation (9:00PM: 16.9 ± 1.5%, 6:00AM: 16.7 ± 1.3% and 11:00AM: 18.1 ± 1.7%, p=NS).
Conclusions: Endothelial-mediated vasodilation is blunted in the early morning in healthy subjects. Impairment of endothelial function in the early morning may have implications for understanding the morning peak in cardiac and vascular events.

1065-175 Effects of Allopurinol on Endothelial Function and Nitrate Tolerance in Type 2 Diabetics With Stable Angina

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Background: Diabetic patients have endothelial dysfunction due to increased oxidative stress. Continuous treatment with nitroglycerin (NTG) increases oxidative stress, and induces not only nitrate tolerance, but also NTG-induced endothelial dysfunction. Xanthine oxidase is known as one of the sources of superoxide. We assessed the effects of allopurinol, a xanthine oxidase inhibitor, on endothelial function, nitrate tolerance, and NTG-induced endothelial dysfunction. **Methods:** Twenty-four type 2 diabetics with stable angina were randomized to receive allopurinol (*Allo group*: n=12, 300 mg/day) or not to receive allopurinol (*Cont group*, n=12). Flow-mediated dilatation (FMD) and NTG-induced dilatation (NID) of brachial artery were measured by using high resolution ultrasound system. These measurements were performed in 12-hour overnight fasting condition at baseline, and then at 1 month after the therapy with allopurinol (1 Mo) and 1 month after the therapy with allopurinol and NTG patch 25 mg/day (2 Mo). **Results:** At baseline, there was no difference in glucose level, HbA1c, FMD and NID between two groups. FMD was significantly increased at 1 Mo in the *allo group*, but was significantly decreased at 2 Mo in the both group. NID did not change at 1 Mo in the both groups, but was significantly decreased at 2 Mo in the both groups. **Conclusion:** Allopurinol improves endothelial function, but does not prevent nitrate tolerance and NTG-induced endothelial dysfunction in type 2 diabetics with stable angina.

Flow-mediated dilatation (FMD) and NTG-induced dilatation (NID)

		Baseline	1 month	2 months
FMD (%)	**Allopurinol**	5.2 +/- 1.1	8.5 +/- 1.8***§**	4.1 +/- 1.2***#**
	Control	5.4 +/- 1.2	5.6 +/- 1.4	4.0 +/- 1.3***#**
NID (%)	**Allopurinol**	14.6 +/- 1.4	14.5 +/- 1.5	9.3 +/- 1.2***#**
	Control	14.8 +/- 1.5	14.7 +/- 1.6	8.7 +/- 1.3***#**

Data are mean+/-SD. *p<0.01 vs Baseline, #p<0.01 vs 1 month, §p<0.01 vs Control group

1065-176 Role of Endothelin-1 and Coronary Flow Reserve in Hypertensive Patients Without Coronary Artery Disease

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Background:
It is suggested that hypertensive patients with angina pectoris and normal coronary arteriograms have reduced coronary flow reserve (CFR) due to microvascular dysfunction. Endothelin-1 (ET-1) is a potent vasoconstrictor, and an important modulator of microvascular function. However, there were few comparative investigations of CFR and ET-1 as a cause of the disease. The aim of this study was to evaluate plasma ET-1 levels and its association with the CFR in symptomatic hypertensive patients without coronary artery disease.
Methods:
A total of 62 patients with essential hypertension who are free of coronary artery disease (28 men and 34 women, mean 61 ± 10 years old) were included in the present study. Coronary artery disease was ruled out by coronary angiogram or exercise stress scintigraphy. Plasma concentrations of ET-1 were measured in patients with having a history of typical angina-like chest pain (n=33) and without symptoms (n=29). CFR was measured using adenosine-triphosphate stress transthoracic Doppler echocardiography. Conventional echocardiography and carotid ultrasonography were performed to assess left ventricular mass index (LVMI) and carotid intima-media thickness (IMT).
Results:
Mean value of plasma ET-1 level was 3.5 ± 1.3 pg/ml, and CFR was 2.49 ± 0.60. Each parameter significantly correlated with the other (r=0.409, p < 0.0001). Mean concentration of ET-1 was higher in symptomatic group than in asymptomatic group (4.0 ± 1.3 pg/ml vs. 2.9 ± 1.1 pg/ml, respectively), while CFR was significantly lower in symptomatic group than in asymptomatic group (2.27 ± 0.50 vs. 2.75 ± 0.62, respectively). Prevalence of LVH (LVM index > 50 g/m$^{2.7}$) was similar between the two groups, but carotid IMT was significantly greater in symptomatic group.
Conclusion:
Plasma ET-1 is raised in hypertensive patients with angina-like chest pain but without coronary artery disease, and is associated with reduced CFR. The current study suggests that the impaired CFR in hypertensive patients is associated with endothelial dysfunction due to subclinical atherosclerosis and ET-1 may play a role in the disease process.